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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,712	11/24/2003	Kenji Sugimoto	245901US0	9928

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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/718,712	SUGIMOTO ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *11-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-10), histone H3 and importin α species (in claims 3 and 9), and chromosome and nuclear membrane species (in claims 2 and 8) in the reply filed on 1/28/2005 is acknowledged. The traversal is on the ground(s) that the Examiner did not provide any reasons or examples to demonstrate the proper restriction between Groups I-III in terms of demonstrating that the groups are independent or distinct. The response further asserts that Examiner did not provide additional reasons or examples to demonstrate why searching the inventions of Groups I-III would be a burden. This is not found persuasive because reasons for the proper restriction of Groups I-III were provided on pages 2-4 of the Office action mailed 12/28/2004. For example, Group II and Group I are related as process of making and product made. However, the cell comprising three or more kinds of fusion genes of three or more different cell division proteins fused to three or more different fluorescent proteins can be made by a materially different process such as random integration of gene trap vectors comprising three or more different fluorescent marker proteins, wherein transcription of an endogenous gene results in the expression of a fusion protein of the endogenous gene and the fluorescent protein, followed by selection for different targeting events in different cell division proteins within the same cell. Furthermore, the inventions of Group I and Group III are related as product and process of use. However, the cell can be used in a materially different process such as the identification of transcription factors that regulate the expression of from the promoters that are operably linked to the fusion genes. Moreover, searching any of the groups together would impose a serious search burden. In the instant case, the search of the cell,

methods of making the cell, and methods of using the cell are not coextensive. The inventions of Groups I-III have separate status in the art as shown by their different classifications. In cases such as this one where different fusion genes are provided in the claims, the genes are searched in the non-patent literature. There may be journal articles that disclose cells comprising fusion genes without disclosing the claimed method of making the cells. Further, the journal articles that disclose cells comprising fusion genes may disclose methods of using said cells other than those of the instant claims. Therefore, searching is not coextensive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. An examination on the merits of claims 1-10 and the elected species of histone H3 and importin α (in claims 3 and 9) and chromosome and nuclear membrane (in claims 2 and 8) follows. It is noted that claims 1 and 7 are generic to both species types.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 2/27/2004, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Specification

The abstract of the disclosure is objected to because it is composed of two paragraphs. The abstract should be written as a single paragraph. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 2, 3, 8 and 9 are objected to because of the following informalities: the claims read on non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 8 are vague and indefinite in that the metes and bounds of the phrase "at least two kinds of nucleus, chromosome, nuclear membrane, centrosome, centromere, spindle, cytoskeleton, heterochromatin and telomere" are unclear. The phrase is unclear in that it can be interpreted as limiting the cell structure which reflects the situation of cell division to one that is present on two kinds of nucleus (e.g. a nucleus obtained from a human or mouse), two kinds of chromosome, etc. Alternatively, the phrase can be interpreted as a Markush-type group limiting the proteins that constitute a cell structure which reflects the situation of cell division to at least two proteins which constitute at least two cellular structures selected from the group consisting of nucleus, chromosome, nuclear membrane, centrosome, centromere, spindle, cytoskeleton, heterochromatin and telomere. Upon reading the instant specification, it appears that Applicant

has intended the cellular structures to comprise a Markush-type group. For the purposes of examination, the list of cellular structures has been interpreted as such a group.

Claims 3 and 9 are vague and indefinite in that the metes and bounds of the phrase "two kinds of histone H3, histone H2B, importin α, lamin B, aurora A, Aurora B, α-tubulin, β-tubulin, γ-tubulin, centromere protein A, centromere protein C, heterochromatin protein 1, survivin, actin, and a telomere protein" are unclear. The phrase is unclear in that that it can be interpreted as limiting the proteins that constitute a cell structure which reflects the situation of cell division to two kinds (e.g. polymorphic variants) of each protein listed, where each of the recited proteins is part of a fusion gene in a cell division-visualized cell. Alternatively, the phrase can be interpreted as a Markush-type group limiting the proteins that constitute a cell structure which reflects the situation of cell division to at least two proteins selected from the list consisting of histone H3, histone H2B, importin α, lamin B, aurora A, Aurora B, α-tubulin, β-tubulin, γ-tubulin, centromere protein A, centromere protein C, heterochromatin protein 1, survivin, actin, and a telomere protein. Upon reading the instant specification, it appears that Applicant has intended the list of proteins to comprise a Markush-type group. For the purposes of examination, the list of proteins has been interpreted as such a group.

Claims 4 and 10 are vague and indefinite in that the metes and bounds of the phrase "two kinds or three or more kinds of green fluorescent proteins, cyan fluorescent proteins, red fluorescent proteins and yellow fluorescent proteins" are unclear. The phrase is unclear in that it can be interpreted as limiting the fluorescent proteins to two kinds of green fluorescent protein (e.g. EGFP and GFP), where each of the recited proteins is part of a fusion gene in a cell division-visualized cell. Alternatively, the phrase can be interpreted as a Markush-type group

limiting the fluorescent proteins to at least two selected from the group consisting of green fluorescent protein, cyan fluorescent protein, red fluorescent protein and yellow fluorescent protein. Upon reading the instant specification, it appears that Applicant has intended the list of proteins to comprise a Markush-type group. For the purposes of examination, the list of fluorescent proteins has been interpreted as such a group.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Sugimoto et al (Cell Structure and Function, Vol. 27, pages 457-467, December 1, 2002; see the entire reference).

Sugimoto et al teach MDA-435 cells (i.e. a mammalian somatic cell) comprising three fusion genes: histone H3 fused to cyan fluorescent protein (CFP-histone H3), importin α fused to red fluorescent protein (DsRed-importinα), and Aurora-A fused to green fluorescent protein (EGFP-Aurora-A) (e.g. page 458, Construction of a human stable cell line MDA-Auro-imp-H3; Figures 2 and 3). CFP-histone H3, DsRed-importinα, and EGFP-Aurora-A localize to the following cell structures: chromosome, nuclear membrane, and centrosome, respectively (e.g. page 459, right column, second full paragraph).

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugimoto et al (Molecular Biology of the Cell, Vol. 13, pages 50a-51a, Abstract 282, November 1, 2002; see the entire abstract).

Sugimoto et al teach a mammalian cell line comprising three fusion genes: histone H3 fused to cyan fluorescent protein (CFP-histone H3), importin α fused to red fluorescent protein (DsRed-importinα), and Aurora-A fused to green fluorescent protein (GFP-Aurora-A) (paragraph bridging pages 50a-51a). CFP-histone H3, DsRed-importinα, and EGFP-Aurora-A localize to the following cell structures: chromosome, nuclear membrane, and centrosome, respectively (paragraph bridging pages 50a-51a).

Regarding claim 6, the human cell taught by Sugimoto et al must be a somatic cell or germ cell, because the human body is composed of somatic cells and germ cells.

Claims 1, 2, 4-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerlich et al (Nature Cell Biology, Vol. 3, pages 852-855, 2001; see the entire reference).

Gerlich et al teach NRK cells (i.e. mammalian somatic cells) comprising three fusion genes: histone H2B fused to cyan fluorescent protein (H2B-CFP), lamin B receptor fused to green fluorescent protein (LBR-GFP), and γ-tubulin fused to red fluorescent protein (γtubulin-RFP) (e.g. page 855, Cells and DNA constructs; Figure 2). H2B-CFP, LBR-GFP, and γtubulin-RFP localize to the following cell structures: chromosome, nuclear membrane, and centrosomes, respectively (e.g. page 853, right column; Figure 2). Furthermore, Gerlich et al teach the use of

the cell to study cell division during late anaphase (e.g. page 853, right column, first full paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerlich et al (Nature Cell Biology, Vol. 3, pages 852-855, 2001; see the entire reference) in view of Kimura et al (The Journal of Cell Biology, Vol. 153, No. 7, pages 1341-1353, 2001; see the entire reference) further in view of Kim et al (The Journal of Biological Chemistry, Vol. 275, No. 30, pages 23139-23145, 2000).

The teachings of Gerlich et al are described above and applied as before.

Gerlich et al do not teach a cell comprising the fusion genes encoding the following fusion proteins: (i) histone H3 fused to a fluorescent protein, and (ii) importin α fused to a fluorescent protein.

Kimura et al teach the replacement of histone H2B coding sequence, in a plasmid encoding a histone H2B-green fluorescent protein fusion protein, with histone H3 coding sequence such that a histone H3-green fluorescent protein (H3-GFP) fusion gene is made (e.g. page 1342, Plasmid Construction, Transfection, and Cell Fusion). Further, Kimura et al teach the transfection of the H3-GFP fusion gene into mammalian somatic cells (e.g. page 1342, Plasmid Construction, Transfection, and Cell Fusion). Moreover, Kimura et al teach that histone H3 is more stably integrated into chromatin as compared to histone H2B in that greater than 80% of histone H3 remains bound permanently to the chromosomes whereas about 53% of histone H2B remains bound permanently (e.g. Figure 7, pages 1351-1352, Transcriptional Activity of the Different Population, Concluding Remarks).

Kim et al teach the fusion gene comprising importin α and green fluorescent protein (GFP) coding sequences (e.g. page 23140, Plasmid Construction and Expression of Fusion Proteins). Further, Kim et al teach the transfection of mammalian somatic CHO-K1 cells, where the Importin α-GFP fusion protein localized to the nucleus (e.g. Figure 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cell comprising fusion genes of Gerlich et al to replace the H2B coding sequence in the H2B-CFP construct taught by Gerlich et al with the H3 sequence of Kimura et al because Gerlich et al teach the use of H2B coding sequence to monitor chromosomes and Kimura et al teach the localization of histone H3-GFP to chromosomes. Further, Kimura et al

specifically teach the replacement of the H2B coding sequence with H3 coding sequence within a fusion protein gene comprising a fluorescent protein. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cell comprising fusion genes of Gerlich et al to include the importin α fusion gene in addition to the fusion genes taught by Gerlich or as a replacement of the coding sequence in the γtubulin-RFP construct because Gerlich et al teach it is within the skill of the art to make cells comprising fluorescent fusion proteins to monitor cell division and Kim et al teach the localization of Importin α-GFP to the nucleus, a cellular structure involved in cell division.

One would have been motivated to make such a modification to include a histone H3-fluorescent protein construct in order to receive the expected benefit of more stable integration of histone H3 into chromosomes as compared to histone H2B as taught by Kimura et al. Further, one would have been motivated to include an importin α-fluorescent protein construct to receive the expected benefit of being able to monitor the nucleus of the cell as taught by Kim et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jennifer Dunston
Examiner
Art Unit 1636

jad

TERRY MCKELVEY
PRIMARY EXAMINER